UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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SIENNA BIOPHARMACEUTICALS, INC.,

Petitioner

v.

RICE UNIVERSITY,

Patent Owner

_____

U.S. Patent No. 6,530,944

Issued: March 11, 2003

Named Inventors: Jennifer L. West, Nancy J. Halas & Leon R. Hirsch

Title: OPTICALLY-ACTIVE NANOPARTICLES FOR USE IN THERAPEUTIC AND DIAGNOSTIC METHODS

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PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 6,530,944 UNDER 37 C.F.R. § 1.68

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EXHIBIT LIST

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1002	U.S. Patent No. 5,226,907 (Tankovich I)
1003	U.S. Patent No. 5,817,089 (Tankovich II)
1004	U.S. Patent No. 6,183,773 (Anderson)
1005	U.S. Patent No. 6,165,440 (Esenaliev)
1006	Declaration of Kenneth S. Suslick, Ph.D.
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1008	'944 Patent Prosecution History
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1010	"40 nm, but not 750 or 1,500 nm, Nanoparticles Enter Epidermal CD1a+ Cells after Transcutaneous Application on Human Skin," A. Vogt et al., Journal of Investigative Dermatology, Vol. 126 (2006) (Vogt).

In accordance with 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42.100 *et seq*., Petitioner Sienna Biopharmaceuticals, Inc. ("Sienna" or "Petitioner") respectfully requests that the Board institute *inter partes* review of claims 1, 6-8 and 12 ("challenged claims") of U.S. Patent 6,530,944 ("the '944 patent"), which is owned by Rice University ("Rice" or "Patent Owner"), and cancel those claims because they are unpatentable in view of prior art patents and printed publications.

I. INTRODUCTION

The five claims challenged in this Petition are all directed to therapeutic methods using light-absorbing nanoparticles. In the methods, the nanoparticles are delivered to the area of interest, such as human tissue. They are then exposed to light at one or more wavelengths that are absorbed by the nanoparticles to generate local heating of cells or tissue. Ex. 1006 [Suslick decl.] at ¶ 30.

As set forth below, the claims of the '944 patent are unpatentable because they recite known methods that were described in printed publications before the effective filing date of the claimed invention, and are obvious because they are nothing more than the result of combining "familiar elements according to known methods" to "yield predictable results." *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 415-16 (2007). As the Supreme Court has held, "when a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement,

the combination is obvious." *Id*. at 417 (*quoting Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 282 (1976) (*reh'g denied*, 426 U.S. 955 (1976))). The key question is whether the alleged improvement "is more than the predictable use of prior art elements according to their established functions." *Id.* at 401. As set forth below, the answer to this question is "no" for the '944 patent because, well before the purported invention, therapeutic methods using light-absorbing nanoparticles were well known and/or obvious. Patents and printed publications predating the purported invention also taught and disclosed therapeutic methods using light-absorbing nanoparticles.

It would have been obvious to a person having ordinary skill in the art to use the teachings of these references to practice the method of the challenged claims. Notably, "the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference...." *In re Keller*, 642 F.2d 413, 425 (CCPA 1981). Rather, "obviousness focuses on what the combined teachings would have suggested." *In re Mouttet*, 686 F.3d 1322, 1330 (Fed. Cir. 2012) (citations omitted).

II. FORMALITIES

A. Notice of Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

The real-parties in interest for this Petition are Sienna Biopharmaceuticals, Inc., 2111 Palomar Airport Rd. #120, Carlsbad, CA 92011; and David Maki, 1014 Market St., Suite 200, Kirkland, WA 98033.

B. Notice of Related Matters (37 C.F.R. § 42.8(b)(2))

There are no other judicial or administrative matters that would directly affect, or be directly affected by, a decision in this proceeding. Petitioner notes that a separate Petition is being concurrently filed to challenge claims of U.S. Patent No. 6,685,730, which shares a common assignee and has overlapping subject matter with the '944 patent, although the patents do not share any priority or other familial relationship.

C. Designation of Lead and Back-up Counsel (37 C.F.R. § 42.8(b)(3))

Lead Counsel: Michael R. Fleming (Reg. No. 67,933)

Backup Counsel: Andrei Iancu (Reg. No. 41,862), Kamran Vakili (Reg. No. 64,825)

Address: Irell & Manella LLP, 1800 Avenue of the Stars, Suite 900, Los Angeles, CA 90067 | Tel: (310) 277-1010 | Fax: (310) 203-7199

D. Service Information (37 C.F.R. § 42.8(b)(4))

Please address all correspondence to the lead and backup counsel above.

Petitioner also consents to email service at: SiennaIPR@irell.com.

E. Payment of Fees (37 C.F.R. § 42.103)

The Office is authorized to charge the required fees, including the fee set forth in 37 C.F.R. § 42.15(a), to Deposit Account No. 09-0946 referencing Docket No. 163301-0001(944IPR), and for any other required fees.

F. Certification of Grounds for Standing (37 C.F.R. § 42.104(a))

Petitioner certifies that the '944 patent is eligible for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review of the challenged claims of the '944 patent on the grounds identified herein.

III. CHALLENGE AND RELIEF REQUESTED

Pursuant to 37 C.F.R. § 42.22(a)(1) and §§ 42.104(b) and (b)(1), Petitioner challenges claims 1-68 of the '944 patent. Petitioner respectfully requests *inter partes* review and cancellation of claims 1, 6-8 and 12 of the '944 patent based on the grounds detailed below.

A. Specific Art and Statutory Ground(s) on Which the Challenges Are Based

Pursuant to 37 C.F.R. § 42.104(b)(2), *inter partes* review of the '944 patent is requested in view of the following references, each of which is prior art to the '944 patent under 35 U.S.C. § 102:

1. Nikolai I. Tankovich, *Hair Removal Device and Method*, U.S. Patent No. 5,226,907 (filed October 29, 1991; issued July 13, 1993) (Tankovich I).

2. Nikolai I. Tankovich, et al., *Skin Treatment Process Using Laser*, U.S. Patent No. 5,817,089 (filed June 12, 1995; issued October 6, 1998) (Tankovich II).

3. Richard R. Anderson, *Targeting of Sebaceous Follicles as a Treatment of Sebaceous Gland Disorders*, U.S. Patent No. 6,183,773 (filed January 4, 1999; issued February 6, 2001) (Anderson).

4. Rinat O. Esenaliev, *Radiation and Nanoparticles for Enhancement of Drug Delivery in Solid Tumors*, U.S. Patent No. 6,165,440 (filed July 9, 1998; issued December 26, 2000) (Esenaliev).

The Tankovich I and Tankovich II references each qualify as prior art under pre-AIA 35 U.S.C. § 102(b) because each was published or issued more than one year prior to the earliest priority date recited by the ’944 patent, February 8, 2000. The Esenaliev and Anderson references qualify under pre-AIA 35 U.S.C. § 102(e) having filing dates of July 9, 1998 and January 4, 1999 respectively. Of these references, only the Esenaliev reference was cited or considered by the PTO during the prosecution of the ’944 patent.

Petitioner requests cancellation of challenged claims 1, 6-8 and 12 under the following statutory grounds:

Ground 1: Claims 1 and 7 are anticipated by Tankovich I under 35 U.S.C. § 102(b)

Ground 2: **Claims 1, 6 and 7 are anticipated by Tankovich II under 35 U.S.C. § 102(b)**

Ground 3: **Claims 1, 6 and 7 are anticipated by Anderson under 35 U.S.C. § 102(e)**

Ground 4: **Claims 1, 6-8 and 12 are anticipated by Esenaliev under 35 U.S.C. § 102(e)**

Ground 5: **Claims 6, 8 and 12 are rendered obvious by Tankovich I in view of Esenaliev under 35 U.S.C. § 103**

Ground 6: **Claims 8 and 12 are rendered obvious by Tankovich II in view of Esenaliev under 35 U.S.C. § 103**

Ground 7: **Claims 8 and 12 are rendered obvious by Anderson in view of Esenaliev under 35 U.S.C. § 103**

Section VII demonstrates, for each of the statutory grounds, that there is a reasonable likelihood that the Petitioner will prevail. *See* 35 U.S.C. § 314(a). Additional explanation and support for each ground is set forth in the expert declaration of Kenneth S. Suslick, Ph.D. Ex. 1006 [Suslick decl.].

IV. THE '944 PATENT

The application leading to the '944 patent was filed on February 8, 2001, and included claims for earlier priority to provisional patent application no. 60/181,109 filed on February 8, 2000 and provisional patent application no.

60/222,437 filed on August 1, 2000. Ex. 1001-1. The references relied upon in this Petition are prior art to the '944 patent because they all predate the filing date of provisional patent application no. 60/181,109, February 8, 2000, the earliest possible priority date for the '944 patent. Tankovich I and Tankovich II are 35 U.S.C. § 102(b) references because they were published more than a year prior to the earliest possible priority date of the '944 patent. Anderson and Esenaliev are 35 U.S.C. § 102(e) references because their application filing dates are prior to the earliest possible priority date of the '944 patent.

A. Representative Claim 1

The crux of the alleged invention of the '944 patent is the straightforward and well-known process of delivering light-absorbing nanoparticles to human tissue and applying light to cause local heating. *See, e.g.*, Ex. 1006 [Suslick decl.] at ¶ 32. For example, claim 1 recites a method "for inducing localized hyperthermia in a cell or tissue" comprising (a) "delivering nanoparticles to said cell or tissue," and (b) "exposing said nanoparticles to infrared radiation under conditions wherein said nanoparticles emit heat upon exposure to said infrared radiation." Ex. 1001 ['944 patent] at 33:53-57.

B. The '944 Patent Disclosure

1. Inducing Localized Hyperthermia In A Cell Or Tissue

The '944 patent describes the "object of the present invention to provide materials and methods for use in cell and tissue therapy," in particular the "primary

object[,] . . . a method for inducing a localized, targeted hyperthermia in such cell and tissue therapy." Ex. 1001 ['944 patent] at 4:47-50. In order to accomplish such localized hyperthermia, "particles are administered to cells and/or tissue, which upon their exposure to light, effect the in vitro or in vivo, local heating of their immediate environment." *Id.* at 4:57-59; Ex. 1006 [Suslick decl.] at ¶ 33.

2. Delivering Nanoparticles To Cell Or Tissue

The '944 patent defines nanoparticle generally, stating, "[a]s used herein, 'nanoparticle' is defined as a particle having a diameter of from 1 to 1000 nanometers, having any size, shape or morphology," and specifies that "'nanoparticle' means one or more nanoparticles." Ex. 1001 ['944 patent] at 6:65-67, 7:7-8. It further states, "[a]s used herein 'delivering' nanoparticles to a location is defined as effecting the placement of the nanoparticles attached to, next to, or sufficiently close to the location such that any heat generated by the nanoparticles is transferred to the location." *Id.* at 6:54-58; Ex. 1006 [Suslick decl.] at ¶ 34.

3. Exposing Nanoparticles To Infrared Radiation, Where Nanoparticles Emit Heat Upon Exposure

The '944 patent describes how "particles are administered to cells and/or tissue, which upon their exposure to light, effect the in vitro or in vivo, local heating of their immediate environment." *Id.* at 4:57-59. It states that "the nanoparticles . . . [are] excited using radiation such as near infrared light

(approximately 800 to 1300 nm)," and that "[u]pon excitation, the nanoshells emit heat." *Id.* at 8:17-21. In one example, highlighting the role of the nanoparticles in heating the local tissue upon exposure, the '944 patent describes how "[e]xposure to the laser in the absence of nanoshells did not induce visible tissue damage," but "tissues … injected with nanoshells before exposure . . . sustained extensive tissue damage." *Id.* at 31:65-32:1; Ex. 1006 [Suslick decl.] at ¶ 35.

V. PERSON HAVING ORDINARY SKILL IN THE ART

A Person Having Ordinary Skill In The Art ("PHOSITA") would generally have had either (i) a Bachelor's degree in chemical engineering, physics, chemistry, materials science, or a similar field, and two or three years of work experience in materials technology, chemical or biomedical research or related fields, or (ii) a Master's degree in chemical engineering, physics, chemistry, materials science, or a similar field and one or two years of work experience in materials technology, chemical or biomedical research or related fields. Ex. 1006 [Suslick decl.] at ¶¶ 18-21.

VI. CLAIM CONSTRUCTION

In an *inter partes* review, the challenged claims must be given their "broadest reasonable construction" in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *see also Cuozzo Speed Techs., LLC v. Lee*, 136 S.Ct. 2131, 2146 (2016) (affirming the broadest reasonable construction

standard). Because of this rule, for the purpose of this *inter partes* review, Petitioner has employed the broadest reasonable construction of the challenged claims throughout this petition. The broadest reasonable construction of claim terms, of course, will often be quite different from the construction those terms would receive in district court claim construction proceedings. *See Agilent Technologies Inc. v. Affymetrix, Inc.*, No. C 06-05958 JW, 2008 WL 7348188, at *5 (N.D. Cal. June 13, 2008). Pursuant to 37 C.F.R. § 42.104(b)(3), the following subsections explain the proper construction of particular claim terms at issue for purposes of this review.

A. "nanoparticles"

The challenged claims of the '944 patent recite the limitation of "nanoparticles." For example, independent claim 1 recites, "delivering **nanoparticles** to said cell or tissue," "exposing said **nanoparticles** to infrared radiation," and "wherein said **nanoparticles** emit heat upon exposure." Ex. 1001 ['944 patent] at 33:53-57. The limitation is also recited by challenged dependent claim 7, "said **nanoparticles** absorb said radiation," and claim 8, "coupling molecules to the **nanoparticles**." *Id.* at 34:4-8; Ex. 1006 [Suslick decl.] at ¶ 43.

The broadest reasonable interpretation ("BRI") of the claim term "nanoparticles" is "particles of any size, shape or morphology having a diameter of from 1 to 1000 nanometers" because that is its plain and ordinary meaning. This is

evidenced, for example, in the definition of "nanoparticle" provided in a standard dictionary: "a microscopic particle whose size is measured in nanometers." Ex. 1009 [Merriam-Webster's] at 824. A particle having a diameter between 1 and 1000 nanometers would typically be measured in units of nanometers, as opposed to a coarser or finer unit. Ex. 1006 [Suslick decl.] at ¶ 44. The plain and ordinary meaning is further corroborated by the definition presented in the specification of the '944 patent. Ex. 1001 ['944 patent] at 6:65-67 ("As used herein, 'nanoparticle' is defined as a particle having a diameter of from 1 to 1000 nanometers, having any size, shape or morphology"); Ex. 1006 [Suslick decl.] at ¶ 44. "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *Trivascular, Inc. v. Samuels*, No. 2015-1631, 2016 WL 463539, at *3 (Fed. Cir. Feb. 5, 2016) (citing *Straight Path IP Grp., Inc. v. Sipnet EU S.R.O.*, 806 F.3d 1356, 1362 (Fed. Cir. 2015)).

B. "infrared radiation"

The challenged claims of the '944 patent recite the limitation of "infrared radiation." For example, independent claim 1 recites, "exposing said nanoparticles to **infrared radiation** . . . wherein said nanoparticles emit heat upon exposure to said **infrared radiation**." Ex. 1001 ['944 patent] at 33:55-57. The limitation is also recited by dependent claim 6, "the infrared radiation is of wavelengths from

800 nm to 1300 nm or from 1600 nm to 1850 nm." *Id.* at 34:1-3; Ex. 1006 [Suslick decl.] at ¶ 45.

The BRI of the claim term "infrared radiation" is "electromagnetic radiation whose wavelength lies in the range from 700 nanometers to 1 millimeter" in accordance with the plain and ordinary meaning of the term. The plain and ordinary meaning, as reflected in the proposed construction, is corroborated by the standard dictionary definition of "infrared radiation": "situated outside the visible spectrum at its red end – used of radiation having a wavelength between about 700 nanometers and 1 millimeter." Ex. 1009 [Merriam-Webster] at 642; Ex. 1006 [Suslick decl.] at ¶ 46. "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *Trivascular, Inc. v. Samuels*, No. 2015-1631, 2016 WL 463539, at *3 (Fed. Cir. Feb. 5, 2016) (citing *Straight Path IP Grp., Inc. v. Sipnet EU S.R.O.*, 806 F.3d 1356, 1362 (Fed. Cir. 2015)).

VII. THERE IS A REASONABLE LIKELIHOOD THAT AT LEAST ONE CLAIM OF THE '944 PATENT IS UNPATENTABLE

Claims 1, 6-8 and 12 of the '944 patent are unpatentable on the following grounds:

Ground	35 U.S.C.	References(s)	Claims
1	§ 102(b)	Tankovich I	1 and 7
2	§ 102(b)	Tankovich II	1, 6 and 7
3	§ 102(e)	Anderson	1, 6 and 7
4	§ 102(e)	Esenaliev	1, 6-8 and 12

5	§ 103(a)	Tankovich I in view of Esenaliev	6, 8 and 12
6	§ 103(a)	Tankovich II in view of Esenaliev	8 and 12
7	§ 103(a)	Anderson in view of Esenaliev	8 and 12

In support of these grounds, the Petition includes a Declaration of Dr. Kenneth Suslick, a nanoparticle and nanochemistry expert. Ex. 1006 [Suslick decl.].

Of the references in this petition, only Esenaliev was before the Examiner during the prosecution of the '944 patent. The Petition does not present the same or substantially the same prior art or arguments previously presented during the prosecution of the '944 patent or any parent applications. Furthermore, the Declaration of Dr. Kenneth Suslick, which provides discussion and analysis of the cited prior art including Esenaliev, was not before the Examiner during prosecution of the '944 patent. Petitioner further notes that the grounds set forth below lack redundancy at least because they include references qualifying as prior art under both 35 U.S.C. § 102(b) and § 102(e).

Pursuant to 37 C.F.R. § 42.104(b)(4), Petitioner provides in the following claim charts a detailed comparison of the claimed subject matter and the prior art specifying where each element of the challenged claims is found in the prior art.

A. Ground 1: Claims 1 And 7 Are Anticipated by Tankovich I Under 35 U.S.C. § 102(b)

As set forth below, Tankovich I teaches the well-known process of delivering light-absorbing nanoparticles to human tissue and applying light to

cause local heating, and teaches all of the elements of independent claim 1 and dependent claim 7. Ex. 1006 [Suslick decl.] at ¶ 48.

1. Tankovich I Teaches All the Limitations of Independent Claim 1

Tankovich I teaches "A method for inducing localized hyperthermia in a cell or tissue," as recited by claim 1. Petitioner submits that the preamble should not be given patentable weight, at least because "the preamble merely recites the purpose of the process [and] the remainder of the claim . . . does not depend on the preamble for completeness and the process steps are able to stand alone." *In re Hirao*, 535 F.2d 67, 70 (CCPA 1976); *see also Intirtool, Ltd. v. Texar Corp.*, 369 F.3d 1289, 1294-96, 70 USPQ2d 1780, 1783-84 (Fed. Cir. 2004) (holding that the preamble of a patent claim directed to a "hand-held punch pliers for simultaneously punching and connecting overlapping sheet metal" was not a limitation of the claim because (i) the body of the claim described a "structurally complete invention" without the preamble, and (ii) statements in prosecution history referring to "punching and connecting" function of invention did not constitute "clear reliance" on the preamble needed to make the preamble a limitation); *Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.*, 246 F.3d 1368, 1374-75 (Fed. Cir. 2001); *Kropa v. Robie*, 187 F.2d 150, 151-52 (CCPA 1951). The preamble here, "[a] method for inducing localized hyperthermia in a cell or tissue," merely recites an intended purpose of the claim, but has no further

substantive relationship to the elements recited by the claim, which stand alone as a structurally complete invention. Therefore, the preamble is undeserving of patentable weight. However, should the Board disagree and deem the preamble as deserving patentable weight, Petitioner notes that Tankovich I is generally directed to hair removal achieved by locally heating hair follicles using nano-scale carbon particles illuminated with electromagnetic radiation. *See*, *e.g.*, Ex. 1002 [Tankovich I] at 1:35-39 ("The skin is illuminated with light at this frequency band at sufficient intensity and duration to kill the follicles of the hair. Specific embodiments produce death of the follicles by heating . . . ."); 2:51-64 ("Operating within the parameters is very important. They have been chosen preferentially to heat the suspension which in turn heats the hair follicles and the blood vessels feeding the follicles but to minimize the heat to the rest of the skin tissue."). Ex. 1006 [Suslick decl.] at ¶ 49.

a) Delivering nanoparticles to said cell or tissue

Tankovich I teaches, "delivering nanoparticles to said cell or tissue," as recited by claim 1. It describes preparing a suspension of carbon nanoparticles in oil and rubbing the mixture into a clean section of skin to infiltrate hair ducts containing the follicles to be heated. *See*, *e.g.*, Ex. 1002 [Tankovich I] at 1:67-2:8 ("First, a laser absorbing carbon suspension is prepared of carbon powder in peach oil. The particle size of the powder is about 10-20 nm . . . . This suspension is

rubbed on the skin with a massaging action so that portions of the carbon suspension infiltrates the hair ducts of the hair that is to be removed . . . .”). Tankovich I’s disclosed particle size range, from 10-20 nanometers, overlaps the size range of “nanoparticles” of 1 to 1000 nanometers, as described in the ’944 patent and discussed above in Section VI.A in relation to claim construction. Ex. 1006 [Suslick decl.] at ¶ 50.

b) Exposing said nanoparticles to infrared radiation under conditions wherein said nanoparticles emit heat upon exposure to said infrared radiation

Tankovich I teaches “exposing said nanoparticles to infrared radiation under conditions wherein said nanoparticles emit heat upon exposure to said infrared radiation,” as recited by claim 1. Tankovich I describes use of a “laser device . . . which has spikes in the range of 10.6 microns,” that is “readily absorbed in carbon.” Ex. 1002 [Tankovich I] at 2:14-18. Electromagnetic radiation of wavelength of 10.6 microns is infrared radiation in the wavelength range of 700 nanometers to 1 millimeter. Ex. 1006 [Suslick decl.] at ¶ 51. The parameters of the radiation “have been chosen to preferentially heat the suspension [of carbon nanoparticles] which in turn heats the hair follicles and the blood vessels feeding the follicles to temperatures high enough to kill the hair follicles[.]” Ex. 1002 [Tankovich I] at 2:51-64. In fact, “a large amount of energy is deposited in the

suspension quickly so that the temperature of the suspension rises rapidly in steps to about above 70°-80° C." *Id.*; Ex. 1006 [Suslick decl.] at ¶ 51.

2. Chart for Claim 1

'944 Claim	Disclosure of Tankovich I
1. A method for inducing localized hyperthermia in a cell or tissue comprising the steps of:	*See*, *e.g.*, Ex. 1002 [Tankovich I], 1:35-39 ("The skin is illuminated with light at this frequency band at sufficient intensity and duration to kill the follicles of the hair. Specific embodiments produce death of the follicles by heating and by photochemical reaction."). *Id.* at 2:51-64 ("Operating within the parameters specified is very important. They have been chosen to preferentially heat the suspension which in turns heats the hair follicles and the blood vessels feeding the follicles to temperatures high enough to kill the hair follicles and the tissue feeding the follicles but to minimize the heat to the rest of the skin tissue. The pulse width is a most important parameter. It must be chosen so that a large amount of energy is deposited in the suspension quickly so that the temperature of the suspension rises rapidly in steps to about above 70°-80° C. This temperature applied for about 1 to 3 seconds is high enough to kill the follicles and/or the vessels feeding the follicles but not high enough to vaporize the oil. "). *Id.* at 3:7-30 (Table 2):

<table>
<tr><td></td><td>

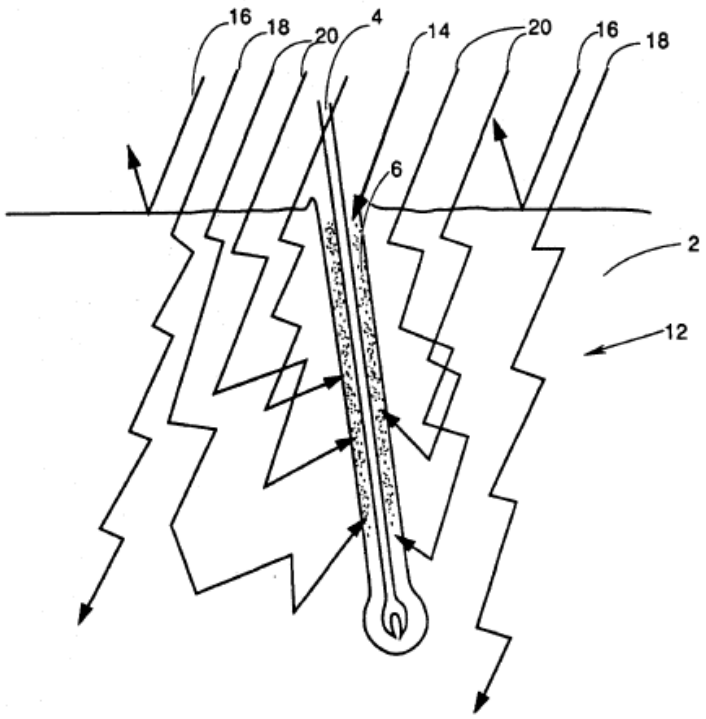
TABLE 2

Heating of hair and carbon oil suspension in hair duct.

Repetition Rate	33 pulses per second
Time between pulses	about 0.03 seconds
Hair duct diameter	0.1 mm
Energy per Pulse	0.1 J
Energy per second	(0.1 J) (33) = 33 J/sec = 3 W
Beam spot	1 cm^2
Hair spacing	130 hairs/cm^2
Distance between hairs	0.1 cm = 1 mm
Assume ¼ of energy goes into hair duct	
Energy per hair per pulse	(0.1 J/130)/4 = 0.00016 J
Volume of hair duct Length 1 mm Diameter 0.1 mm	
Vol. $= l\,\pi \left(\frac{D}{2}\right)^2 =$	(0.1 cm) $\pi \left(\frac{0.01}{2}\right)^2 = 0.0000078\ cm^3$
Density of oil and hair =	0.9 gm/cm^3
Mass of oil & hair	0.000007 gm
Specific heat of oil & hair assume	4 J/gm °C.
Temperature rise per pulse, $\Delta T = \frac{Q}{mc}$	$\frac{0.00016\ J}{(0.000007\ gm)4J/gm\ °C.} \approx 5°\ C.$

</td></tr>
<tr><td>**[1.a]** delivering nanoparticles to said cell or tissue and</td><td>*See*, *e.g.*, Ex. 1002 [Tankovich I], 1:67-2:8 (“First, a laser absorbing carbon suspension is prepared of carbon powder in peach oil. The particle size of the powder preferably is about 10-20 nm and its concentration preferably is about 15% to 20% by volume. A clean section of skin is depicted in FIG. 2A. This suspension is rubbed on the skin with a massaging action so that portions of the carbon suspension infiltrates the hair ducts of the hair that is [to] be removed as shown in FIG. 2B.”).</td></tr>
<tr><td>**[1.b]** exposing said nanoparticles to infrared radiation under conditions wherein said nanoparticles emit heat upon exposure to</td><td>*See*, *e.g.*, Ex. 1002 [Tankovich I], 2:14-18 (“The laser device used in this preferred embodiment is a CO_2 pulse laser which has the spikes in the range of 10.6 microns. Light in this range will pass through the surface of the skin of a fair skin person and is readily absorbed in carbon. ”)

Id. at 2:51-64 (“Operating within the parameters specified is very important. They have been chosen to preferentially heat the suspension which in turns heats the hair follicles and the blood vessels feeding the follicles to temperatures high enough to kill the hair follicles and the tissue feeding the</td></tr>
</table>

said infrared radiation.	follicles but to minimize the heat to the rest of the skin tissue. The pulse width is a most important parameter. It must be chosen so that a large amount of energy is deposited in the suspension quickly so that the temperature of the suspension rises rapidly in steps to about above 70°-80° C. This temperature applied for about 1 to 3 seconds is high enough to kill the follicles and/or the vessels feeding the follicles but not high enough to vaporize the oil.”). *Id.* at Fig. 3  FIG. 3

3. Tankovich I Teaches All the Limitations of Claim 7

Claim 7: Tankovich I teaches, “wherein said nanoparticles absorb said radiation,” as recited by claim 7. *See*, *e.g.*, Ex. 1002 [Tankovich I] at 2:16-18 (“Light in this range . . . is readily absorbed by the carbon.”); *Id.* at 1:67-2:1 (“[A]

laser absorbing carbon suspension is prepared of carbon powder in peach oil. The particle size is about 10-20 nm . . . ."); Ex. 1006 [Suslick decl.] at ¶ 53.

4. Chart for Claim 7

'944 Claim	Disclosure of Tankovich I
7. The method of claim 1 wherein said nanoparticles absorb said radiation.	*See*, *e.g.*, Ex. 1002 [Tankovich I], 2:14-18 ("The laser device used in this preferred embodiment is a CO_2 pulse laser which has the spikes in the range of 10.6 microns. Light in this range will pass through the surface of the skin of a fair skin person and is readily absorbed in carbon.") *Id.* at 1:67-2:8 ("First, a laser absorbing carbon suspension is prepared of carbon powder in peach oil. The particle size of the powder preferably is about 10-20 nm and its concentration preferably is about 15% to 20% by volume. A clean section of skin is depicted in FIG. 2A. This suspension is rubbed on the skin with a massaging action so that portions of the carbon suspension infiltrates the hair ducts of the hair that is [to] be removed as shown in FIG. 2B.").

B. Ground 2: Claims 1, 6 and 7 Are Anticipated By Tankovich II Under 35 U.S.C. § 102(b)

As set forth below, Tankovich II teaches the well-known process of delivering light-absorbing nanoparticles to human tissue and applying light to cause local heating, and teaches all of the elements of independent claim 1 and dependent claims 6 and 7. Ex. 1006 [Suslick decl.] at ¶ 55.

1. Tankovich II Teaches All the Limitations of Independent Claim 1

Tankovich II teaches "A method for inducing localized hyperthermia in a cell or tissue," as recited by claim 1. Petitioner submits that the preamble should

not be given patentable weight, at least because "the preamble merely recites the purpose of the process [and] the remainder of the claim . . . does not depend on the preamble for completeness and the process steps are able to stand alone." *In re Hirao*, 535 F.2d 67, 70 (CCPA 1976); *see also Intirtool, Ltd. v. Texar Corp.*, 369 F.3d 1289, 1294-96, 70 USPQ2d 1780, 1783-84 (Fed. Cir. 2004) (holding that the preamble of a patent claim directed to a "hand-held punch pliers for simultaneously punching and connecting overlapping sheet metal" was not a limitation of the claim because (i) the body of the claim described a "structurally complete invention" without the preamble, and (ii) statements in prosecution history referring to the "punching and connecting" function of invention did not constitute "clear reliance" on the preamble needed to make the preamble a limitation); *Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.*, 246 F.3d 1368, 1374-75 (Fed. Cir. 2001); *Kropa v. Robie*, 187 F.2d 150, 151-52 (CCPA 1951). The preamble here, "[a] method for inducing localized hyperthermia in a cell or tissue," merely recites an intended purpose of the claim, but has no further substantive relationship to the elements recited by the claim, which stand alone as a structurally complete invention. Therefore, the preamble is undeserving of patentable weight. However, should the Board disagree and deem the preamble as deserving patentable weight, Petitioner notes that Tankovich II is generally directed to skin resurfacing, hair removal, and/or acne treatment achieved by

administering a topical solution containing nanoparticles, such as graphite particles, and exposing them to radiation absorbed by the particles to caused localized heating thereof. *See*, *e.g.*, Ex. 1003 [Tankovich II] at 5:64-67 ("The damage to the tissue appears to be the . . . result of . . . the heating effect of the hot carbon particles and oil . . ."); *Id.* at 6:27-34 ("The carbon particles within or in the vicinity of the sebaceous glands are heated to vaporization temperatures . . . . Energy released in the process results in full or partial destruction of epithelium tissue . . . ."). Ex. 1006 [Suslick decl.] at ¶ 56.

a) Delivering nanoparticles to said cell or tissue

Tankovich II teaches, "delivering nanoparticles to said cell or tissue," as recited by claim 1. It describes a process where, "[t]he first step . . . is to topically apply a layer of carbon solution to the skin surface . . . comprised of 1 micron graphite powder in baby oil," the particles thus having diameter in the range of 1 to 1000 nm in accordance with the claim construction set forth above in Section VI.A. Ex. 1003 [Tankovich II] at 3:47-50. Ex. 1006 [Suslick decl.] at ¶ 57.

b) Exposing said nanoparticles to infrared radiation under conditions wherein said nanoparticles emit heat upon exposure to said radiation

Tankovich II teaches "exposing said nanoparticles to infrared radiation under conditions wherein said nanoparticles emit heat upon exposure to said radiation," as recited by claim 1. It describes, "irradiat[ing] the skin surface with

Nd:YAG laser pulses of about 3 J/cm^2 at a wavelength of 1.06 μm," noting that the "[g]raphite [nanoparticles are] very absorptive of laser energy at the 1.06 μm wavelength." Ex. 1003 [Tankovich II] at 4:3-8. Electromagnetic radiation of wavelength of 1.06 μm is infrared radiation in the wavelength range of 700 nanometers to 1 millimeter. Tankovich II further describes how "[t]he damage to the tissue appears to be the combined result of both the heating effect of the hot carbon particles and oil and possibly some mechanical damage due to the kinetic energy of the particles and fragments." Ex. 1003 [Tankovich II] at 5:64-67. Ex. 1006 [Suslick decl.] at ¶ 58.

2. Chart for Claim 1

'944 Claim	**Disclosure of Tankovich II**
1. A method for inducing localized hyperthermia in a cell or tissue comprising the steps of	*See*, *e.g.*, Ex. 1003 [Tankovich II], 5:64-67 ("The damage to the tissue appears to be the combined result of both the heating effect of the hot carbon particles and oil and possibly some mechanical damage due to the kinetic energy of the particles and fragments."). *Id.* at 6:27-34 ("The carbon particles within or in the vicinity of the sebaceous glands are heated to vaporization temperatures which causes the particles to fracture violently or vaporize. Energy released in the process results in full or partial destruction of epithelium tissue making up the surface of the inside wall of the sebaceous glands which tissue, produces the sebum. This results in either death or reduced effectiveness of the sebaceous glands in the section of skin treated.").
[1.a] delivering nanoparticles to said cell or tissue and	*Id.* at 3:47-50 ("The first step of this preferred embodiment is to topically apply a layer of carbon solution to the skin surface as shown in FIG. 3B. The solution is comprised of 1 micron graphite powder in

	baby oil.").
[1.b] exposing said nanoparticles to infrared radiation under conditions wherein said nanoparticles emit heat upon exposure to said infrared radiation.	*Id*. at 4:3-8 ("The next step is to irradiate the skin surface with Nd:YAG laser pulses of about 3 J/cm^2 at a wavelength of 1.06 μm. Pulse frequency is about 5 Hz but we scan the beam so that each location is subjected to pulses at a frequency of about 1 Hz. Graphite is very absorptive of laser energy at the 1.06 μm wavelength.") *Id.* at 5:64:67 ("The damage to the tissue appears to be the combined result of both the heating effect of the hot carbon particles and oil and possibly some mechanical damage due to the kinetic energy of the particles and fragments.").

3. Tankovich II Teaches All the Limitations of Claims 6 and 7

Claim 6: Tankovich II teaches "the infrared radiation is of wavelengths from 800 nm to 1300 nm or from 1600 nm to 1850 nm," as recited by claim 6. For example, it states, "The next step is to irradiate the skin surface with Nd:YAG laser pulses of about 3 J/cm^2 at a wavelength of 1.06 μm." Ex. 1003 [Tankovich II] at 4:3-4. A wavelength of 1.06 μm corresponds to 1060 nm. Ex. 1006 [Suslick decl.] at ¶ 60.

Claim 7: Tankovich II teaches "said nanoparticles absorb said radiation," as recited by claim 7. It describes how the graphite nanoparticles are "very absorptive of laser energy at the 1.06 μm wavelength," and how "[t]he energy is deposited in a few nanoseconds so there is no time for the heat to diffuse; therefore, the particle explodes violently upon being illuminated by the pulse. Ex. 1003 [Tankovich II], 4:3-19. Ex. 1006 [Suslick decl.] at ¶ 61.

4. Chart for Claims 6 and 7

'944 Claim	Disclosure of Tankovich II
6. The method of claim 1 wherein the infrared radiation is of wavelengths from 800 nm to 1300 nm or from 1600 nm to 1850 nm.	*See*, *e.g.*, Ex. 1003 [Tankovich II], 4:3-8 ("The next step is to irradiate the skin surface with Nd:YAG laser pulses of about 3 J/cm^2 at a wavelength of 1.06 μm. Pulse frequency is about 5 Hz but we scan the beam so that each location is subjected to pulses at a frequency of about 1 Hz. Graphite is very absorptive of laser energy at the 1.06 μm wavelength.")
7. The method of claim 1 wherein said nanoparticles absorb said radiation.	*See*, *e.g.*, Ex. 1003 [Tankovich II] at 4:3-19 ("The next step is to irradiate the skin surface with Nd:YAG laser pulses of about 3 J/cm^2 at a wavelength of 1.06 μm. Pulse frequency is about 5 Hz but we scan the beam so that each location is subjected to pulses at a frequency of about 1 Hz. Graphite is very absorptive of laser energy at the 1.06 μm wavelength. . . . The energy is deposited in a few nanoseconds so there is no time for the heat to diffuse; therefore, the particle explodes violently upon being illuminated by the pulse.")

C. Ground 3: Claims 1, 6 and 7 Are Anticipated By Anderson Under 35 U.S.C. § 102(e)

As set forth below, Anderson teaches the well-known process of delivering light-absorbing nanoparticles to human tissue and applying light to cause local heating, and teaches all of the elements of independent claim 1 and dependent claims 6 and 7. Ex. 1006 [Suslick decl.] at ¶ 63.

1. Anderson Teaches All the Limitations of Independent Claim 1

Anderson teaches "A method for inducing localized hyperthermia in a cell or

tissue," as recited by claim 1. Petitioner submits that the preamble should not be given patentable weight, at least because "the preamble merely recites the purpose of the process [and] the remainder of the claim . . . does not depend on the preamble for completeness and the process steps are able to stand alone." *In re Hirao*, 535 F.2d 67, 70 (CCPA 1976); *see also Intirtool, Ltd. v. Texar Corp.*, 369 F.3d 1289, 1294-96, 70 USPQ2d 1780, 1783-84 (Fed. Cir. 2004) (holding that the preamble of a patent claim directed to a "hand-held punch pliers for simultaneously punching and connecting overlapping sheet metal" was not a limitation of the claim because (i) the body of the claim described a "structurally complete invention" without the preamble, and (ii) statements in prosecution history referring to "punching and connecting" function of invention did not constitute "clear reliance" on the preamble needed to make the preamble a limitation); *Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.*, 246 F.3d 1368, 1374-75 (Fed. Cir. 2001); *Kropa v. Robie*, 187 F.2d 150, 151-52 (CCPA 1951). The preamble here, "[a] method for inducing localized hyperthermia in a cell or tissue," merely recites an intended purpose of the claim, but has no further substantive relationship to the elements recited by the claim, which stand alone as a structurally complete invention. Therefore, the preamble is undeserving of patentable weight. However, should the Board disagree and deem the preamble as deserving patentable weight, Petitioner notes that Anderson is generally directed to

"[p]hotothermal activation of an energy activatable material caus[ing] the material to be heated, thereby heating the local area, preferably selectively with a significant temperature increase of such that unwanted material, e.g., tissues, oils, bacteria, viruses, dirt, etc. such that the surrounding tissue remains unaffected[.]" Ex. 1004 [Anderson], 6:3-11. Ex. 1006 [Suslick decl.] at ¶ 64.

a) Delivering nanoparticles to said cell or tissue

Anderson teaches, "delivering nanoparticles to said cell or tissue," as recited by claim 1. It describes "[s]uitable materials . . . includ[ing] metal oxides, such as aluminum oxide, iron oxides, carbon particles (graphite and amorphous carbon particles) and natural and synthetic chromophores." Ex. 1004 [Anderson], 5:47-67. It goes on to state that "[d]elivery of the energy activatable material . . . to the follicle matrix can be achieved by topical application, injection, liposome encapsulation technology, massage, iontophoresis or ultrasonic technology, or other means for delivery of compounds into the dermal region of the skin[.]" *Id.* at 11:19-25. Anderson states that "[a] sufficient amount of the material infiltrates the psilosebaceous unit." *Id.* at 4:25-29. A PHOSITA would understand, from Anderson's discussion of infiltration of the psilosebaceous unit and/or delivery by liposome encapsulation technology, that the disclosed energy activatable material, including "carbon particles," should be of size in the range from 1 to 5000 nanometers. *See*, *e.g.*, Ex. 1010 [Vogt] at Abstract ("[F]low cytometry after

transcutaneous application of 40, 750, or 1,500 nm nanoparticles on human skin samples revealed that only 40 nm particles entered epidermal LCs [Langerhans cells]. . . . [O]nly 40 nm particles deeply penetrate into vellus hair openings and through the follicular epithelium."); Ex. 1006 [Suslick decl.] at ¶ 65.

b) Exposing said nanoparticles to infrared radiation under conditions wherein said nanoparticles emit heat upon exposure to said radiation

Anderson teaches "exposing said nanoparticles to infrared radiation under conditions wherein said nanoparticles emit heat upon exposure to said radiation," as recited by claim 1. It discusses how "[t]he introduction of a energy activatable material in sebaceous glands followed by exposure to energy (light) with a wavelength that corresponds to the absorption peak of the chromophore, will increase the local absorption of light in tissue and lead to selective thermal damage of the sebaceous glands." Ex. 1004 [Anderson], 10:33-38. It states that "[t]hese materials can be stimulated by various energy sources, e.g., electromagnetic sources, such as . . . infrared light." *Id.* at 5:40-44. Ex. 1006 [Suslick decl.] at ¶ 66.

2. Chart for Claim 1

'944 Claim	**Disclosure of Anderson**
1. A method for inducing localized hyperthermia in a cell or tissue comprising the steps	*See*, *e.g.*, Ex. 1004 [Anderson], 6:3-11 ("The term "photothermal" interaction (excitation or stimulation) is art recognized and is intended to include interactions which are due to conversion of energy into heat. Photothermal activation of an energy activatable material

of	causes the material to be heated, thereby heating the local area, preferably selectively with a significant temperature increase of such that unwanted material, e.g., tissues, oils, bacteria, viruses, dirt, etc. such that the surrounding tissue remains unaffected[.]").
[1.a] delivering nanoparticles to said cell or tissue and	*See*, *e.g.*, Ex. 1004 [Anderson], 5:47-67 ("Suitable materials useful in the invention include metal oxides, such as aluminum oxide, iron oxides, carbon particles (graphite and amorphous carbon particles) and natural and synthetic chromophores. The term "chromophore" is art recognized and is intended to include those compounds which absorb energy at a given wavelength, often by sites of unsaturation, carbon-oxygen bonds, and/or charged species, or combinations thereof. Suitable chromophoric groups include nitro groups, azo, quinoids, alkylene units, carbonyls, esters, alkynes, aldehydes, carboxylic acids, and those groups associated with $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions. Preferred energy activatable materials include laser sensitive dyes, for example, methylene blue, indocyanine green and those in U.S. Pat. No. 4,651,739, issued Mar. 24, 1987, the entire contents of which are incorporated herein by reference. Preferred dyes are those dyes which are activated by laser stimulation. Preferred laser sensitive dyes are those which are FDA approved. A preferred dye, a laser sensitive dye, is methylene blue. In one embodiment, the laser sensitive dye is not indocyanine green. In another embodiment, the energy activatable material is not carbon particles."). *Id.* at 11:19-25 ("Delivery of the energy activatable material, preferably methylene blue or other FDA approved dyes, to the follicle matrix can be achieved by topical application, injection, liposome encapsulation technology, massage, iontophoresis or ultrasonic technology, or other means for delivery of compounds into the dermal region of the skin, e.g., pharmaceutically acceptable carriers.").
[1.b] exposing said nanoparticles to	*See*, *e.g.*, Ex. 1004 [Anderson], 10:33-38 ("The introduction of a energy activatable material in

infrared radiation under conditions wherein said nanoparticles emit heat upon exposure to said infrared radiation.	sebaceous glands followed by exposure to energy (light) with a wavelength that corresponds to the absorption peak of the chromophore, will increase the local absorption of light in tissue and lead to selective thermal damage of sebaceous glands."). *Id.*at 5:37-46 ("The phrase 'energy activatable material' is intended to include those agents which, when stimulated by energy from an energy source, e.g., a laser source, become energetically stimulated, e.g., photothermally or photochemically. These materials can be stimulated by various energy sources, e.g., electromagnetic sources, such as a continuous wave source, a laser source, flashlamp, ultraviolet light, microwaves, infrared light, etc."). *Id.*at 7:58-65 ("It is highly preferred to use wavelengths of the optical spectrum in which natural skin pigments exhibit weaker absorption (to minimize heating at other sites), and which penetrate well to the anatomic depth of the infundibulum and/or sebaceous glands. The orange, red, and near-infrared wavelength region (600-1200 nm) is therefore most appropriate. At these wavelengths, there is very little absorption by natural skin pigments other than melanin.").

3. Anderson Teaches All the Limitations of Claims 6 and 7

Claim 6: Anderson teaches "the infrared radiation is of wavelengths from 800 nm to 1300 nm or from 1600 nm to 1850 nm," as recited by claim 6. For example, it describes the desirability of employing radiation having wavelengths in this range in order to minimize undesirable absorption in surrounding tissues. Ex. 1004 [Anderson] at 9:32-36 ("Another desirable property of thermal and photochemical energy activatable material is an absorption spectrum in the range

of 600-1300 nm; this minimizes surrounding blood from absorbing light intended for the material[.]"). Ex. 1006 [Suslick decl.] at ¶ 68.

Claim 7: Anderson teaches "said nanoparticles absorb said radiation," as recited by claim 7. The energy activatable material is described in Anderson as having an "absorption spectrum in the range of 600-1300 nm." Ex. 1004 [Anderson], 9:33-34. It states, "[t]he introduction of a energy activatable material in sebaceous glands followed by exposure to energy (light) with a wavelength that corresponds to the absorption peak of the chromophore, will increase the local absorption of light in tissue[.]" *Id.* at 10:33-38. Ex. 1006 [Suslick decl.] at ¶ 69.

4. Chart for Claims 6 and 7

'944 Claim	**Disclosure of Anderson**
6. The method of claim 1 wherein the infrared radiation is of wavelengths from 800 nm to 1300 nm or from 1600 nm to 1850 nm.	*See*, *e.g.*, Ex. 1004 [Anderson], 7:58-65 ("It is highly preferred to use wavelengths of the optical spectrum in which natural skin pigments exhibit weaker absorption (to minimize heating at other sites), and which penetrate well to the anatomic depth of the infundibulum and/or sebaceous glands. The orange, red, and near-infrared wavelength region (600-1200 nm) is therefore most appropriate. At these wavelengths, there is very little absorption by natural skin pigments other than melanin."). *Id.* at 9:32-36 ("Another desirable property of thermal and photochemical energy activatable material is an absorption spectrum in the range of 600-1300 nm; this minimizes surrounding blood from absorbing light intended for the material (hemoglobin absorbs most strongly at the violet end

	of the spectrum).”).
7. The method of claim 1 wherein said nanoparticles absorb said radiation.	*See*, *e.g.*, Ex. 1004 [Anderson], 10:33-38 (“The introduction of a energy activatable material in sebaceous glands followed by exposure to energy (light) with a wavelength that corresponds to the absorption peak of the chromophore, will increase the local absorption of light in tissue and lead to selective thermal damage of sebaceous glands.”). *Id.*at 9:32-36 (“Another desirable property of thermal and photochemical energy activatable material is an absorption spectrum in the range of 600-1300 nm; this minimizes surrounding blood from absorbing light intended for the material (hemoglobin absorbs most strongly at the violet end of the spectrum).”).

D. Ground 4: Claims 1, 6-8 and 12 Are Anticipated By Esenaliev Under 35 U.S.C. § 102(e)

As set forth below, Esenaliev teaches the well-known process of delivering light-absorbing nanoparticles to human tissue and applying light to cause local heating, and teaches all of the elements of independent claim 1 and dependent claims 6-8 and 12. Ex. 1006 [Suslick decl.] at ¶ 71.

1. Esenaliev Teaches All the Limitations of Independent Claim 1

Esenaliev teaches “A method for inducing localized hyperthermia in a cell or tissue,” as recited by claim 1. Petitioner submits that the preamble should not be given patentable weight, at least because “the preamble merely recites the purpose of the process [and] the remainder of the claim . . . does not depend on the preamble for completeness and the process steps are able to stand alone.” *In re*

Hirao, 535 F.2d 67, 70 (CCPA 1976); *see also Intirtool, Ltd. v. Texar Corp.*, 369 F.3d 1289, 1294-96, 70 USPQ2d 1780, 1783-84 (Fed. Cir. 2004) (holding that the preamble of a patent claim directed to a "hand-held punch pliers for simultaneously punching and connecting overlapping sheet metal" was not a limitation of the claim because (i) the body of the claim described a "structurally complete invention" without the preamble, and (ii) statements in prosecution history referring to the "punching and connecting" function of invention did not constitute "clear reliance" on the preamble needed to make the preamble a limitation); *Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.*, 246 F.3d 1368, 1374-75 (Fed. Cir. 2001); *Kropa v. Robie*, 187 F.2d 150, 151-52 (CCPA 1951). The preamble here, "[a] method for inducing localized hyperthermia in a cell or tissue," merely recites an intended purpose of the claim, but has no further substantive relationship to the elements recited by the claim, which stand alone as a structurally complete invention. Therefore, the preamble is undeserving of patentable weight. However, should the Board disagree and deem the preamble as deserving patentable weight, Petitioner notes that Esenaliev is directed to inducing "local heating of the particles by pulsed electromagnetic radiation result[ing] in perforation of tumor blood vessels, microconvection in the interstitium, and perforation of cancer cell membrane." Ex. 1005 [Esenaliev] at 1:66-2:3. *See also Id.* at 6:25-44 ("It is known that severe local heating of strongly absorbing particles

. . . produces vapor microbubbles upon irradiation by short pulses, which results in mechanical and thermal damage to the materials."). Ex. 1006 [Suslick decl.] at ¶ 72.

a) Delivering nanoparticles to said cell or tissue

Esenaliev teaches, "delivering nanoparticles to said cell or tissue," as recited by claim 1. For example, it describes "nanoparticles or microparticles [that] can be metal particles, carbon particles, graphite particles," or others that have "a diameter from about 0.1 nm to about 7000 nm." Ex. 1005 [Esenaliev] at 2:24-29. This corresponds to the '944 patent's definition of nanoparticles "having a diameter of from 1 to 1000 nanometers." Ex. 1001 ['944 patent] at 6:65-67. Esenaliev goes on to describe the nanoparticles being "selectively delivered to tumor blood vessel walls." Ex. 1005 [Esenaliev] at 1:65-66. Ex. 1006 [Suslick decl.] at ¶ 73.

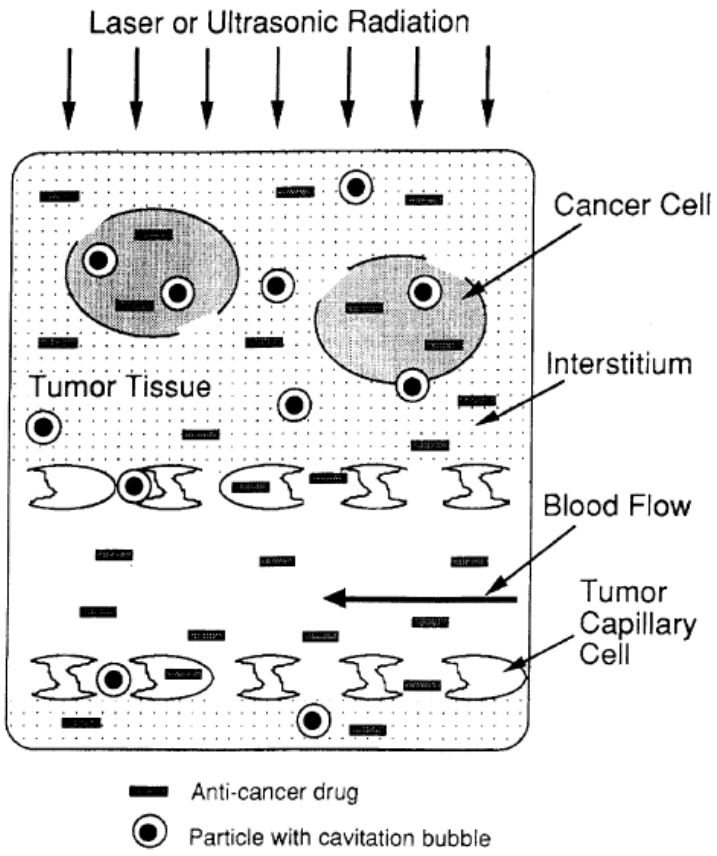
b) Exposing said nanoparticles to infrared radiation under conditions wherein said nanoparticles emit heat upon exposure to said radiation

Esenaliev teaches "exposing said nanoparticles to infrared radiation under conditions wherein said nanoparticles emit heat upon exposure to said radiation," as recited by claim 1. It describes "local heating of the particles by pulsed electromagnetic radiation," in particular stating that its system "utilizes nanosecond Nd:YAG laser radiation with the wavelength of 1064 nm to induce local heating of strongly absorbing particles," which falls within the wavelength

range of 700 nanometers to 1 millimeter for infrared radiation. Ex. 1005 [Esenaliev] at 1:66-67; 7:4-7. Ex. 1006 [Suslick decl.] at ¶ 74. Esenaliev also discusses the advantages of using "[o]ptical radiation in the near infra-red and visible spectral ranges" due to "low attenuation in tissues." *Id.* at 9:39-42. Ex. 1006 [Suslick decl.] at ¶ 74.

2. Chart for Claim 1

'944 Claim	**Disclosure of Esenaliev**
1. A method for inducing localized hyperthermia in a cell or tissue comprising the steps of	*See*, *e.g.*, Ex. 1005 [Esenaliev], 1:66-2:3 ("[L]ocal heating of the particles by pulsed electromagnetic radiation results in perforation of tumor blood vessels, microconvection in the interstitium, and perforation of cancer cell membrane."). *Id.* at 7:4-7 ("The system utilizes nanosecond Nd:YAG laser radiation with the wavelength of 1064 nm to induce local heating of strongly absorbing particles."). *Id.*at 6:25-44 ("It is known that severe local heating of strongly absorbing particles in transparent optical materials produces vapor microbubbles upon irradiation by short laser pulses, which results in mechanical and thermal damage to the materials. Local heating of a strongly absorbing particle in a medium can be induced, if laser pulse duration is shorter than the time of heat diffusion. . . . Local heating of exogenous strongly absorbing nanoparticles by short (nanosecond) and ultrashort (picosecond) laser pulses results in explosive evaporation of blood in tumor vasculature and formation of microbubbles.")
[1.a] delivering	*See*, *e.g.*, Ex. 1005 [Esenaliev], 1:63-66 ("The particles

nanoparticles to said cell or tissue and	can be attached to antibodies directed against antigens in tumor vasculature and selectively delivered to tumor blood vessel walls. ") *Id.* at 2:24-29 ("The nanoparticles or microparticles can be metal particles, carbon particles, graphite particles, polymer particles loaded with an absorbing dye, liquid particles loaded with an absorbing dye or porous particles having gas-filled pores. The nanoparticle has a diameter from about 0.1 nm to about 7000 nm."). *Id.* at Fig. 1b  FIG. 1b
[1.b] exposing said nanoparticles to infrared radiation under conditions	*See*, *e.g.*, Ex. 1005 [Esenaliev], 1:66-2:3 ("[L]ocal heating of the particles by pulsed electromagnetic radiation results in perforation of tumor blood vessels, microconvection in the interstitium, and perforation of

wherein said nanoparticles emit heat upon exposure to said infrared radiation.	cancer cell membrane.”). *Id.* at 2:30-32 (“Preferably, the radiation is optical pulsed radiation generated from a laser or non-laser source. Specifically, the optical radiation is in the spectral range from 0.2 μm to 2 μm . . . .”). *Id.* at 7:4-7 (“The system utilizes nanosecond Nd:YAG laser radiation with the wavelength of 1064 nm to induce local heating of strongly absorbing particles.”). *Id.* at 9:39-47 (“Optical radiation in the near infra-red and visible spectral range (so-called ‘therapeutic window’: λ=600-1300 nm) has low attenuation in tissues. Therefore, it can induce local heating of the strongly absorbing particles in deeply located tumors without damage to irradiated tissue surface. For example, absorption and scattering coefficients of breast tissue equal to 0.05-0.08 cm^{-1} and 5.0-9.0 cm^{-1}, respectively, in the near infra-red spectral range. ”) *Id.* at Fig. 1b

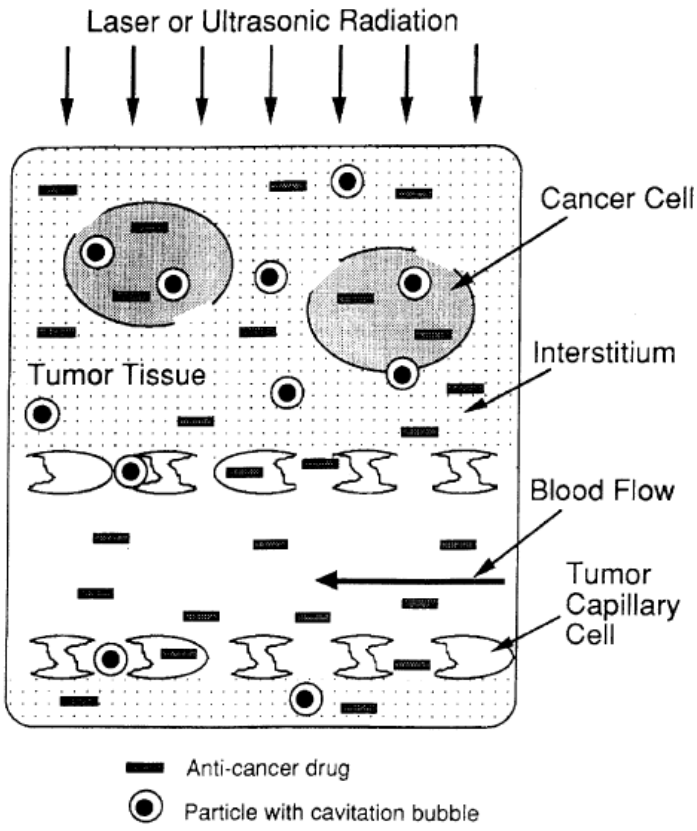


FIG. 1b

3. Esenaliev Teaches All the Limitations of Claims 6-8 and 12

Claim 6: Esenaliev teaches "the infrared radiation is of wavelengths from 800 nm to 1300 nm or from 1600 nm to 1850 nm," as recited by claim 6. For example, it states that its system "utilizes nanosecond Nd:YAG laser radiation with a wavelength of 1064 nm to induce local heating of strongly absorbing particles." Ex. 1005 [Esenaliev] at 7:4-7. In another example, it describes using "optical radiation in the spectral range from 0.2 μm to 2 μm," which corresponds to 200 nm to 2000 nm, overlapping the claimed range. *Id.* at 2:30-32. In both disclosures,

Esenaliev discusses wavelength ranges overlapping the wavelength range of infrared radiation. Ex. 1006 [Suslick decl.] at ¶ 76.

Claim 7: Esenaliev teaches "said nanoparticles absorb said radiation," as recited by claim 7. It describes how "[t]he system utilizes nanosecond Nd:YAG laser radiation . . . to induce local heating of strongly absorbing particles." Ex. 1005 [Esenaliev] at 7:4-7. Ex. 1006 [Suslick decl.] at ¶ 77.

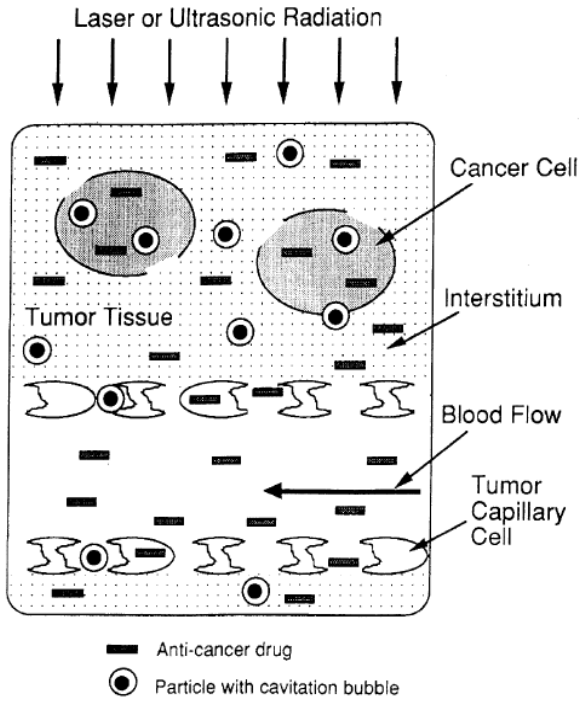
Claim 8: Esenaliev teaches "coupling molecules to the nanoparticles wherein said molecules specifically bind to the cell or tissue," as recited by claim 8. Esenaliev is generally directed to using electromagnetic radiation in conjunction with strongly absorbing nanoparticles "for enhancement of drug delivery in solid tumors." Ex. 1005 [Esenaliev] at 1:62-63. It discusses how "[t]he particles can be attached to antibodies directed against antigens in tumor vasculature and selectively delivered to tumor blood vessel walls." *Id.* at 1:63-66. Those antibodies are the molecules to which the nanoparticles are coupled to specifically bind to tumor blood vessel tissue. Ex. 1006 [Suslick decl.] at ¶ 78.

Claim 12: Esenaliev teaches "said cell is a cancer cell," as recited by claim 12. As noted, Esenaliev is generally directed to using electromagnetic radiation in conjunction with strongly absorbing nanoparticles "for enhancement of drug delivery in solid tumors." Ex. 1005 [Esenaliev] at 1:62-63. The resulting heating causes "perforation of cancer cell membrane[s]" and thereby "enhance[s] delivery

of macromolecular therapeutic agents from the blood into cancer cells[.]" *Id.* at 2:1-5. Ex. 1006 [Suslick decl.] at ¶ 79.

4. Chart for Claims 6-8 and 12

'944 Claim	Disclosure of Esenaliev
6. The method of claim 1 wherein the infrared radiation is of wavelengths from 800 nm to 1300 nm or from 1600 nm to 1850 nm.	*See*, *e.g.*, Ex. 1005 [Esenaliev], 7:4-7 ("The system utilizes nanosecond Nd:YAG laser radiation with the wavelength of 1064 nm to induce local heating of strongly absorbing particles."). *Id.* at 2:30-32 ("Preferably, the radiation is optical pulsed radiation generated from a laser or non-laser source. Specifically, the optical radiation is in the spectral range from 0.2 μm to 2 μm . . . .").
7. The method of claim 1 wherein said nanoparticles absorb said radiation.	*See*, *e.g.*, Ex. 1005 [Esenaliev], 7:4-7 ("The system utilizes nanosecond Nd:YAG laser radiation with the wavelength of 1064 nm to induce local heating of strongly absorbing particles.").
8. The method of claim 1 further comprising the step of coupling molecules to the nanoparticles wherein said molecules specifically bind to the cell or tissue.	*See*, *e.g.*, Ex. 1005 [Esenaliev], 1:60-66 ("The present invention is directed to a method or system of utilizing the interaction of electromagnetic pulses or ultrasonic radiation with nanoparticles and microparticles for enhancement of drug delivery in solid tumors. The particles can be attached to antibodies directed against antigens in tumor vasculature and selectively delivered to tumor blood vessel walls.").
12. The method of claim 1 wherein said cell is a cancer cell.	*See*, *e.g.*, Ex. 1005 [Esenaliev], 1:60-2:6 ("The present invention is directed to a method or system of utilizing the interaction of electromagnetic pulses or ultrasonic radiation with nanoparticles and microparticles for enhancement of drug delivery in solid tumors. The particles can be attached to antibodies directed against antigens in tumor vasculature and selectively delivered to tumor

	blood vessel walls. Cavitation induced by ultrasonic waves or local heating of the particles by pulsed electromagnetic radiation results in perforation of tumor blood vessels, microconvection in the interstitium, and perforation of cancer cell membrane. This method provides enhanced delivery of macromolecular therapeutic agents from the blood into cancer cells with minimal thermal and mechanical damage to normal tissues.”). *See*, *e.g.*, *Id.* at Fig. 1b  FIG. 1b

E. Ground 5: Claims 6, 8 And 12 Are Rendered Obvious By Tankovich I In View Of Esenaliev Under 35 U.S.C. § 103(a)

As set forth below, Tankovich I in view of Esenaliev teaches all the limitations of claims 6, 8 and 12. And as shown in the claim chart below, Tankovich I in view of Esenaliev teaches the well-known process of delivering

light-absorbing nanoparticles to human tissue and applying light to cause local heating, and renders obvious all of the elements of dependent claims 6, 8 and 12. Ex. 1006 [Suslick decl.] at ¶ 81.

Claim 6: The combination of Tankovich I and Esenaliev teaches "the infrared radiation is of wavelengths from 800 nm to 1300 nm or from 1600 nm to 1850 nm," as recited by claim 6. The teaching of Tankovich I for independent claim 1 is discussed above in Section VII.A.1 and the teaching of Esenaliev for dependent claim 6 is discussed above in Section VII.D.3, and are both fully incorporated by reference herein and not repeated for brevity.

Claim 8: The combination of Tankovich I and Esenaliev teaches "coupling molecules to the nanoparticles wherein said molecules specifically bind to the cell or tissue," as recited by claim 8. The teaching of Tankovich I for independent claim 1 is discussed above in Section VII.A.1 and the teaching of Esenaliev for dependent claim 8 is discussed above in Section VII.D.3, and are both fully incorporated by reference herein and not repeated for brevity.

Claim 12: The combination of Tankovich I and Esenaliev teaches "said cell is a cancer cell," as recited by claim 12. The teaching of Tankovich I for independent claim 1 is discussed above in Section VII.A.1 and the teaching of Esenaliev for dependent claim 12 is discussed above in Section VII.D.3, and are both fully incorporated by reference herein and not repeated for brevity.

1. Chart for Claims 6, 8 and 12

'944 Claim	Disclosure of Tankovich I in view of Esenaliev
6. The method of claim 1 wherein the infrared radiation is of wavelengths from 800 nm to 1300 nm or from 1600 nm to 1850 nm.	*See* Tankovich I and Esenaliev disclosures above for Sections VII.A.1-2 [claim 1] and VII.D.3-4 [claim 6].
8. The method of claim 1 further comprising the step of coupling molecules to the nanoparticles wherein said molecules specifically bind to the cell or tissue.	*See* Tankovich I and Esenaliev disclosures above for Sections VII.A.1-2 [claim 1] and VII.D.3-4 [claim 8].
12. The method of claim 1 wherein said cell is a cancer cell.	*See* Tankovich I and Esenaliev disclosures above for Sections VII.A.1-2 [claim 1] and VII.D.3-4 [claim 12].

2. Reasons for Combinability for Claims 6, 8 and 12

A PHOSITA would have had reasons to use aspects of Esenaliev's system for targeted delivery of nanoparticles to tissues and for treating cancer within Tankovich I's system for hair removal using locally heated nanoparticles. Both Tankovich I and Esenaliev discuss the delivery of nanoparticles specifically to the skin. Ex. 1002 [Tankovich I] at 1:67-2:8; Ex. 1005 [Esenaliev] at 2:16-19. In particular, Tankovich I describes the destruction of undesirable skin tissue (*i.e.*, hair and follicle) using localized heating via irradiated nanoparticles, and Esenaliev similarly describes destroying skin cancers using the same localized heating by irradiating nanoparticles applied to the skin. Ex. 1002 [Tankovich I] at 1:67-2:8; Ex. 1005 [Esenaliev] at 2:16-19. It would have been obvious to a PHOSITA to extend Tankovich I's destruction of hair follicles to include Esenaliev's destruction

of skin cancers. Ex. 1006 [Suslick decl.] at ¶ 86. Both Tankovich I and Esenaliev disclose therapeutic systems having a high degree of similarity in structure, purpose and operation. For example, both are directed to the use of nanoparticles capable of absorbing electromagnetic radiation, which are introduced to human tissue, and exposed to such radiation in order to induce a localized heating effect. Ex. 1002 [Tankovich I] at 1:67-2:8, 2:14-18, 2:51-64, Fig. 3; Ex. 1005 [Esenaliev] at 1:63-2:3, 2:24-32, 7:4-7, 9:39-47, Fig. 1b; Ex. 1006 [Suslick decl.] at ¶ 86.

Although Tankovich I discusses a particular embodiment employing laser light having wavelength of 10.6 microns, it specifically describes the desirability of using light that "will pass through the surface of the skin" to be absorbed by the nanoparticles, and explains that laser parameters may be varied "to best fit the skin and hair types of the patients." Ex. 1002 [Tankovich I] at 2:14-20. Accordingly, a PHOSITA would have found it obvious to try other laser wavelengths, such as those described in claim 6 of the '944 patent, in order to target nanoparticles while avoiding tissue. Ex. 1006 [Suslick decl.] at ¶ 87. In particular, a PHOSITA would have looked to analogous art such as Esenaliev describing radiation in the "so-called 'therapeutic window': λ=600-1300nm . . . [that] can induce local heating of the strongly absorbing particles . . . without damage to irradiated tissue surface." Ex. 1005 [Esenaliev] at 9:39-44; Ex. 1006 [Suslick decl.] at ¶ 87

Furthermore, Tankovich I describes the goal of targeting tissues with nanoparticles in order to induce localized heating without damaging surrounding tissues. For example, it describes its technique for delivering nanoparticles "to make the skin surface clean but to leave the hair pores contaminated with the carbon suspension." Ex. 1002 [Tankovich I] at 2:9-11. It also describes the advantage of such targeted delivery, "to preferentially heat the suspension which in turn heats the hair follicles . . . enough to kill the hair follicles . . . but to minimize the heat to the rest of the skin tissue." *Id.* at 2:52-57. It would therefore have been obvious for a PHOSITA to improve Tankovich I's system by applying the known technique described in analogous art Esenaliev of coupling the nanoparticles to molecules that specifically bind to the targeted tissues (Ex. 1005 [Esenaliev] at 1:60-66), predictably yielding the desired result described in Tankovich I of targeting tissues of interest in order to minimize damage to surrounding tissues. Ex. 1006 [Suslick decl.] at ¶ 88.

With regard to claim 12, it would have also have been obvious for a PHOSITA to modify Tankovich I's method of delivering radiation-absorbing nanoparticles to skin with the teaching of Esenaliev to deliver the same type of radiation-absorbing particles to cancer cells. As noted above, both references discuss targeting tissues within the skin. Ex. 1002 [Tankovich I] at 1:67-2:8; Ex. 1005 [Esenaliev] at 2:16-19. Esenaliev specifically addresses targeting cancer

cells and describes the use of molecules coupled to the nanoparticles to facilitate such targeting. Ex. 1005 [Esenaliev] at 1:60-2:6, Fig. 1b. Accordingly, all elements of claim 12 were present in the prior art, and a PHOSITA could have combined them according to the methods described in Tankovich I and Esenaliev to yield the predictable result of delivering the nanoparticles to the cancer cells and inducing localized heating therein. Ex. 1006 [Suslick decl.] at ¶ 89.

F. Ground 6: Claims 8 And 12 Are Rendered Obvious By Tankovich II In View Of Esenaliev Under 35 U.S.C. § 103(a)

As set forth below, Tankovich II in view of Esenaliev teaches all the limitations of claims 8 and 12. And as shown in the claim chart below, Tankovich II in view of Esenaliev teaches the well-known process of delivering light-absorbing nanoparticles to human tissue and applying light to cause local heating, and renders obvious all of the elements of dependent claims 8 and 12. Ex. 1006 [Suslick decl.] at ¶ 90.

Claim 8: The combination of Tankovich II and Esenaliev teaches "coupling molecules to the nanoparticles wherein said molecules specifically bind to the cell or tissue," as recited by claim 8. The teaching of Tankovich II for independent claim 1 is discussed above in Section VII.B.1 and the teaching of Esenaliev for dependent claim 8 is discussed above in Section VII.D.3, and are both fully incorporated by reference herein and not repeated for brevity.

Claim 12: The combination of Tankovich II and Esenaliev teaches "said cell is a cancer cell," as recited by claim 12. The teaching of Tankovich II for independent claim 1 is discussed above in Section VII.B.1 and the teaching of Esenaliev for dependent claim 12 is discussed above in Section VII.D.3, and are both fully incorporated by reference herein and not repeated for brevity.

1. Chart for Claims 8 and 12

'944 Claim	**Disclosure of Tankovich II in view of Esenaliev**
8. The method of claim 1 further comprising the step of coupling molecules to the nanoparticles wherein said molecules specifically bind to the cell or tissue.	*See* Tankovich II and Esenaliev disclosures above for Sections VII.B.1-2 [claim 1] and VII.D.3-4 [claim 8].
12. The method of claim 1 wherein said cell is a cancer cell.	*See* Tankovich II and Esenaliev disclosures above for Sections VII.B.1-2 [claim 1] and VII.D.3-4 [claim 12].

2. Reasons for Combinability for Claims 8 and 12

A PHOSITA would have had reasons to use aspects of Esenaliev's system for targeted delivery of nanoparticles to tissues and for treating cancer within Tankovich II's system for skin treatments using locally heated nanoparticles. Both Tankovich II and Esenaliev discuss skin treatments via delivery of radiation-absorbing nanoparticles specifically to the skin. Ex. 1003 [Tankovich II] at 3:47-50; Ex. 1005 [Esenaliev] at 2:16-19. In particular, Tankovich II describes treating and mitigating skin disorders, such as acne and seborrhea, by localized heating using irradiated nanoparticles, and Esenaliev describes treating skin cancers also

by localized heating with irradiated nanoparticles. Ex. 1003 [Tankovich II] at 2:54-58; Ex. 1005 [Esenaliev] at 2:16-19. It would have been obvious to a PHOSITA to extend Tankovich II's treatment of skin disorders to include Esenaliev's treatment of skin cancer. Ex. 1006 [Suslick decl.] at ¶ 94. The therapeutic systems disclosed in these references have a high degree of similarity in structure, purpose and operation. For example, both are directed to the use of nanoparticles capable of absorbing electromagnetic radiation, which are introduced to human tissue, and exposed to such radiation in order to induce a localized heating effect. Ex. 1003 [Tankovich II] at 3:47-50, 4:3-8; Ex. 1005 [Esenaliev] at 1:63-2:3, 2:24-32, 7:4-7, 9:39-47, Fig. 1b; Ex. 1006 [Suslick decl.] at ¶ 94.

Tankovich II describes selective delivery of the radiation-absorbing nanoparticles to targeted tissues, "between the superficial epidermal cells, into hair ducts in the skin and into and/or adjacent to sebaceous glands." Ex. 1003 [Tankovich II] at 2:65-67. It also points to possible dangers associated with improperly targeted laser treatments, including "pain and undesired burning, . . . bleeding and scarring." *Id.* at 2:6-8. A PHOSITA would therefore have been motivated to apply the known technique described in analogous art Esenaliev of coupling the nanoparticles to molecules that specifically bind to the targeted tissues (Ex. 1005 [Esenaliev] at 1:60-66), predictably yielding the desired result described

in Tankovich II of targeting tissues of interest in order to minimize damage to surrounding tissues. Ex. 1006 [Suslick decl.] at ¶ 95.

With regard to claim 12, it would have also have been obvious for a PHOSITA to modify Tankovich II's method of delivering radiation-absorbing nanoparticles to skin with the teaching of Esenaliev to deliver the same type of radiation-absorbing particles to cancer cells. As noted above, both references discuss targeting tissues within the skin. Ex. 1003 [Tankovich II] at 3:47-50; Ex. 1005 [Esenaliev] at 2:16-19. Esenaliev specifically addresses targeting cancer cells and describes the use of molecules coupled to the nanoparticles to facilitate such targeting. Ex. 1005 [Esenaliev] at 1:60-2:6, Fig. 1b. Accordingly, all elements of claim 12 were present in the prior art, and a PHOSITA could have combined them according to the methods described in Tankovich II and Esenaliev to yield the predictable result of delivering the nanoparticles to the cancer cells and inducing localized heating therein. Ex. 1006 [Suslick decl.] at ¶ 96.

G. Ground 7: Claims 8 And 12 Are Rendered Obvious By Anderson In View Of Esenaliev Under 35 U.S.C. § 103(a)

As set forth below, Anderson in view of Esenaliev teaches all the limitations of claims 8 and 12. And as shown in the claim chart below, Anderson in view of Esenaliev teaches the well-known process of delivering light-absorbing nanoparticles to human tissue and applying light to cause local heating, and renders

obvious all of the elements of dependent claims 8 and 12. Ex. 1006 [Suslick decl.] at ¶ 97.

Claim 8: The combination of Anderson and Esenaliev teaches "coupling molecules to the nanoparticles wherein said molecules specifically bind to the cell or tissue," as recited by claim 8. The teaching of Anderson for independent claim 1 is discussed above in Section VII.C.1 and the teaching of Esenaliev for dependent claim 8 is discussed above in Section VII.D.3, and are both fully incorporated by reference herein and not repeated for brevity.

Claim 12: The combination of Anderson and Esenaliev teaches "said cell is a cancer cell," as recited by claim 12. The teaching of Anderson for independent claim 1 is discussed above in Section VII.C.1 and the teaching of Esenaliev for dependent claim 12 is discussed above in Section VII.D.3, and are both fully incorporated by reference herein and not repeated for brevity.

1. Chart for Claims 8 and 12

'944 Claim	**Disclosure of Anderson in view of Esenaliev**
8. The method of claim 1 further comprising the step of coupling molecules to the nanoparticles wherein said molecules specifically bind to the cell or tissue.	*See* Anderson and Esenaliev disclosures above for Sections VII.C.1-2 [claim 1] and VII.D.3-4 [claim 8].
12. The method of claim 1 wherein said cell is a cancer cell.	*See* Anderson and Esenaliev disclosures above for Sections VII.C.1-2 [claim 1] and VII.D.3-4 [claim 12].

2. Reasons for Combinability for Claims 6, 8 and 12

A PHOSITA would have had reasons to use aspects of Esenaliev's system for targeted delivery of nanoparticles to tissues and for treating cancer within Anderson's system for skin disorders using locally heated nanoparticles. Both Anderson and Esenaliev discuss treatment of skin disorders by delivering radiation-absorbing nanoparticles specifically to the skin. Ex. 1004 [Anderson] at 1:46-50, 11:19-25; Ex. 1005 [Esenaliev] at 2:16-19. In particular, Anderson discusses "curing skin disorders" by localized heating using irradiated nanoparticles, and Esenaliev discusses treating skin cancers using the same local heating with irradiated nanoparticles. Ex. 1004 [Anderson] at 1:46-50; Ex. 1005 [Esenaliev] at 2:16-19. It would have been obvious to a PHOSITA to extend Anderson's treatment of skin disorders to include Esenaliev's treatment of skin cancer. Ex. 1006 [Suslick decl.] at ¶ 101. Anderson and Esenaliev also exhibit a high degree of similarity in structure, purpose and operation for their disclosed therapeutic methods, both describing the use of radiation-absorbing nanoparticles that are introduced to human tissue and exposed to radiation to induce a localized heating. Ex. 1004 [Anderson] at 5:37-67, 7:58-65, 10:33-38, 11:19-25; Ex. 1005 [Esenaliev] at 1:63-2:3, 2:24-32, 7:4-7, 9:39-47, Fig. 1b; Ex. 1006 [Suslick decl.] at ¶ 101.

With regard to the limitation of coupling molecules to the nanoparticles to improve their delivery to target tissues, Anderson discusses its desire to achieve "selective photothermolysis or controlled skin ablation." Ex. 1004 [Anderson] at 1:46-47. In describes the use of "an energy activatable material, adapted to accumulate selectively in the infundibulum and/or the sebaceous gland," which are the tissues to be targeted for selective photothermolysis. *Id.* at 9:61-63. Anderson also discusses possible techniques to achieve the desired selective delivery of the energy activatable material to the targeted tissues, including "liposome encapsulation technology" and "pharmaceutically acceptable carriers." *Id.* at 11:22-25. Anderson also describes the goal of its controlled delivery of nanoparticles to the targeted tissues, "such that localized destruction to the undesired sebaceous gland disorder occurs with little or no non-specific necrosis of surrounding tissue." *Id.* at 8:55-58. A PHOSITA would therefore have been motivated to apply the known technique described in analogous art Esenaliev of coupling the nanoparticles to molecules that specifically bind to the targeted tissues (Ex. 1005 [Esenaliev] at 1:60-66), predictably yielding the desired result described in Anderson of targeting tissues of interest in order to minimize damage to surrounding tissues. Ex. 1006 [Suslick decl.] at ¶ 102.

Regarding claim 12, it would have also have been obvious for a PHOSITA to modify Anderson's method of delivering radiation-absorbing nanoparticles to

skin with the teaching of Esenaliev to deliver the same type of radiation-absorbing particles to cancer cells. As noted above, both references discuss targeting skin tissues and curing disorders within the skin. Ex. 1004 [Anderson] at 1:46-50, 11:19-25; Ex. 1005 [Esenaliev] at 2:16-19. Esenaliev specifically addresses targeting cancer cells and describes the use of molecules coupled to the nanoparticles to facilitate such targeting. Ex. 1005 [Esenaliev] at 1:60-2:6, Fig. 1b. Accordingly, all elements of claim 12 were present in the prior art, and a PHOSITA could have combined them according to the methods described in Anderson and Esenaliev to yield the predictable result of delivering the nanoparticles to the cancer cells and inducing localized heating therein. Ex. 1006 [Suslick decl.] at ¶ 103.

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CERTIFICATE OF SERVICE

I hereby certify, pursuant to 37 C.F.R. sections 42.6 and 42.105, that a complete copy of the Petition for Inter Partes Review of U.S. Patent No. 6,530,944 and Exhibits 1001 through 1010 are being served by Priority Mail Express on the 7th day of October, 2016, the same day as the filing of the above-identified documents in the United States Patent and Trademark Office/Patent Trial and Appeal Board, to the Assignee of record as reflected in the USPTO patent assignment recordation database,

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CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24

Pursuant to 37 C.F.R. § 42.24 (d), I certify that the present paper contains 12,191 words as counted by the word-processing program used to generate the brief. This total does not include the tables of contents and authorities, the caption page, table of exhibits, signature blocks, certificate of service, or this certificate of word count.

Dated: October 7, 2016

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